

## Applications of capsule dosing techniques for use in dry powder inhalers

Dry powder inhaler (DPI) devices that utilize two-piece capsules as the dose-holding system can require specialized dosing equipment to fill the capsules. Such products are known as 'premetered' because they contain previously measured doses in a dose carrier (the capsule). The capsule is either inserted into the device during manufacture or by the patient prior to use. The dose is inhaled directly from the device/premetered unit by the patient. Regardless of DPI design, the most crucial attributes are the reproducibility of the discharged dose and the particle size distribution of the drug within that dose. Filling inhalation powders into capsules often requires specialized equipment in order to handle the very low weights that are often contained in each dose. The equipment typically needs to incorporate in-process checks to confirm the filling process has been correctly performed, with the ability to reject any under- or over-filled capsules, in line with established quality criteria. In the majority of cases, such processing equipment is maintained in a temperature and humidity controlled environment to avoid moisture uptake and potential powder aggregation and, in particular, to ensure the powder is free flowing on introduction into the capsule. This ensures that the emitted dose is maximized and controlled according to industry guidelines and that the fine particle fraction provides an optimum clinical benefit. Several methods of dosing precise doses of powder into capsules are available and include dosator technology and tamp processes, as well as equipment that utilize the 'pepper-shaker' or 'pepper-pot' principle for the accurate dispensing of powders. This article reviews the suitability of each method with respect to dosing inhalation powder into capsules for use in DPI devices, and discusses why the pepper-pot principle could offer a number of clear benefits.

Many disorders affecting the lungs such as asthma and chronic obstructive pulmonary disease are treated by inhaling locally acting bronchodilators to increase the air flow as well as corticosteroids to reduce inflammation. There are a number of systems for delivery of these drugs to the lung but the most common inhaler types are breath-actuated **dry powder inhalers** (DPIs) and metered dose inhalers. The former is a popular choice with patients because they can better co-ordinate dosing with their breathing pattern. In addition, DPIs have been shown to function equally as well as metered dose inhalers in treating patients with acute symptoms of chronic obstructive pulmonary disease [1].

Since inhalation of therapies can be used as a fast-acting route into the general circulation avoiding first-pass metabolism, the use of DPIs has long held promise as an alternative to needle injection for administering peptide- and protein-based therapies. A recent report suggests that locally acting drugs for the treatment of lung diseases delivered by DPIs show bioequivalence to drugs delivered by other methods [2].

Despite initial setbacks with some inhaled drugs via this route for systemic activity, there still remains enthusiasm for developing new inhalation treatments, and studies are ongoing looking at using DPIs to treat cystic fibrosis [3] and diabetes [4], and for delivering drugs such as antibiotics [5].

A two-piece **capsule** is frequently used as the dose-holding system for the DPI, enabling patients to check whether the dose has been taken successfully by viewing the empty capsule shell. Additionally, patients can carry their DPIs with the requisite number of capsules for daily or weekly therapy.

Capsules for use in DPIs have traditionally been hard two-piece gelatin capsules and these have been used successfully in marketed DPIs for over 30 years. Gelatin capsules can be filled using established automated capsule-filling equipment, and are widely available.

Capsules produced from hydroxypropyl methylcellulose (HPMC), such as Vcaps® capsules (**FIGURE 1**), can be readily used in DPIs. HPMC capsules are relatively inert to chemical reaction with the drug substance and lactose-based

### David Edwards

Capsugel, Granta Park,  
Great Abington, Cambridgeshire,  
CB2 16GP, UK  
Tel.: +44 130 464 4780  
E-mail: [david.edwards2@pfizer.com](mailto:david.edwards2@pfizer.com)

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**Key Terms**

**Dry powder inhaler:** Device for delivering a drug dose to the lungs.

**Capsule:** Outer casing made of gelatin or hypromellose that can be filled with a powder or liquid drug dose.

**Dosator:** Method of dosing capsules using mechanical or vacuum compaction and discharging, or vacuum suction and discharging to fill capsules.



Figure 1. Vcaps® capsules.

formulations [6]; they can be easily pierced to allow optimal and reproducible release of the drug formulation from the capsule, and have low moisture content so they can be used with drugs and formulations that are hygroscopic or moisture sensitive. HPMC capsules have also been shown to be less likely to shrink or become brittle when stored under low humidity conditions [7].

It is important that the powder in the capsule containment system retains free-flowing properties during manufacture and storage. Powder formulations consist either of the active pharmaceutical ingredient (API) or as the API blended with a larger particle size carrier such as lactose. Capsules used in DPIs are typically filled with less than 40 mg of powder. Indeed, it is arguable that there is a trend towards low-fill-weight systems as APIs are becoming more potent and so a lower drug mass is required to give a therapeutic benefit.

In order to produce the large numbers of capsules required for use in DPIs, automated capsule filling has become standard practice over the past 30 years. Automated capsule filling has the advantage of keeping losses of costly drugs through spilling or manual weighing errors to a minimum. The use of automated capsule fillers is also safe for the process operator as many can be incorporated within effective containment systems that reduce the formation of airborne drug particles in the proximity of the equipment thereby preventing the continued inhalation of such drugs by the process operator.

### Standard dosator technology

Automated filling systems that use **dosator** technology were first described in the 1970s [8,9]. Current systems rely on dosator heads with mechanical compaction and discharging. While current dosator filling systems have changed

significantly in design, they still retain many of the basic principles of the original systems. The ModU C Capsule Filling and Closing Machine (Harro Höfliger, Helmholtzstraße, Germany) and G250 Capsule Filler (MG2, Bologna, Italy) consist of a rotating hopper on a platform into which the powder to be filled is dispensed and lightly compacted. The dosator head is located above the powder hopper and contains hollow dosing tubes with dosing pistons within the dosing tube. In order to fill a capsule with powder, the dosing tube is plunged into the powder, the dosing piston is pulled back and a plug of powder is collected and held within the dosing tube. The dosator head transfers the dosing tube containing the powder plug to a position above the capsule shell and the dosing piston then discharges the plug into the capsule shell. The final stage is the addition of the other half of the capsule shell. The amount of powder dispensed using this method is determined by the level of the dosing piston within the dosing tube, the diameter of the dosing piston and the depth to which the dosing tube is immersed in the powder bed.

The rotating hopper container, pistons and dosator head can be easily removed for cleaning and decontamination between each batch of different powders. However, use of a powder bed can lead to some drug/powder wastage because it is difficult to fill the entire contents of the rotating hopper as the dosator tubes do need to be immersed to a fixed depth in the powder bed necessitating the discarding of some powder during the cleaning process.

Compaction-based dosator systems allow capsules to be filled with powder over the range of 10 to 500 mg, but use of larger size 00 and 000 capsules allows filling at a significantly higher level. The relative standard deviation (RSD) of this type of dosing system is approximately 2% and the process is capable of between 3000 and 200,000 capsules per hour, dependent on equipment scale, making this type of technology useful for the manufacture of products for small-scale Phase I clinical studies through to full-scale manufacturing.

### Vacuum drum filler

A principle example of this technology for device powder filling is the Harro Höfliger Omnidose, which can be used as a station option on their Modu-C capsule filler. This has a special head for filling low doses of powders down to 1 mg that uses a vacuum system. The dose of powders is metered by special cavities in a cylinder that rotates in the bottom of the powder hopper.

### Vacuum dosators

There are also dosator systems that use vacuum compaction to secure powder within the dosing tube prior to discharge into the capsule. These systems also have a rotating powder hopper on a platform containing the powder, but in this case the powder is not compacted. The dosing tube is immersed into the powder and the plug of powder collected by vacuum suction when the dosing piston is withdrawn. The dosator head transfers the dosing tube containing the powder plug to a position above the capsule shell and the dosing piston then pushes the plug into the capsule shell. The amount of powder dispensed using this method is determined by the distance the dosing piston is withdrawn when immersed in the powder bed and the diameter of the dosing piston.

Vacuum-based dosator systems can be used for filling powder masses over a similar weight range and RSD as compaction-based dosator systems. The technology is also suitable for small scale Phase I clinical trials through to full-scale manufacturing.

From a process efficiency perspective, capsule filling based on dosator technology can require time for set-up in order to dispense different powders into capsules. Such systems depend on a mechanical discharging that must be reset, recalibrated and retested each time a new or different batch of capsules is run. Additionally, using a powder bed can lead to some compound wastage, as noted previously.

A key disadvantage of dosator systems is that the filling technology is typically limited to approximately 10 mg. Highly potent drugs need to be blended with a carrier material (lactose) for accurate dosing. Blending an API with lactose is potentially quite time consuming with regards to developing the formulation and carrying out the required stability studies. Another potential issue is that dosator filling does lead to a degree of powder compaction within the capsule as the plug must have sufficient strength to withstand the transport of the dosator head to a position above the capsule prior to discharge of the dosator contents. However, an essential requirement for capsule contents for use with a DPI is that the powder should be free flowing and free of aggregates. Therefore, dosator technologies that can lead to aggregate formation may not be ideal for all inhalation formulations and work may be required to ensure that the powder plug can be formed at a sufficiently low compression

force to easily disintegrate under the conditions generated within the capsule both during handling by the patient and particularly during the inhalation manoeuvre.

Additionally, as most dosator-based filling systems are large and nonmodular, many cannot be equipped with temperature and humidity control units and need to be housed in a general area that can provide such control, which can be costly to run and maintain. Poor control over temperature and humidity can lead to moisture uptake by the formulation and potentially the formation of aggregates giving lower emitted doses of drug from the DPI and a reduction in the amount of drug depositing in the lungs.

### Tamp filling

Automated **tamp filling** systems for capsule dosing have been in use for some years [10,11]. Today's systems rely on using tamping pins that push up and down within the powder bed so that a unit dose is transferred into a dosing disc. This dose from the disk is then ejected into the capsule body.

On a tamping machine, there is a circular rotating indexing hopper. The dosing disc is the base of the powder hopper, has six sets of holes and is available in a range of thicknesses. There are six sets of tamping fingers corresponding to the number of holes in the dosing disc. Five of the sets of tamping fingers are raised and lowered in the powder bed. The movement of these sets of fingers is adjusted to give different amounts of penetration into the holes in the dosing disc. Powder, which flows into the holes during indexing, is compacted by the movement of

#### Key Term

**Tamp filling:** Technique of dosing capsules using pins, which push up and down through a powder bed so that a dose is transferred into a dosing disc.



Figure 2. The Xcelodose® 600 S precision powder microdosing system.

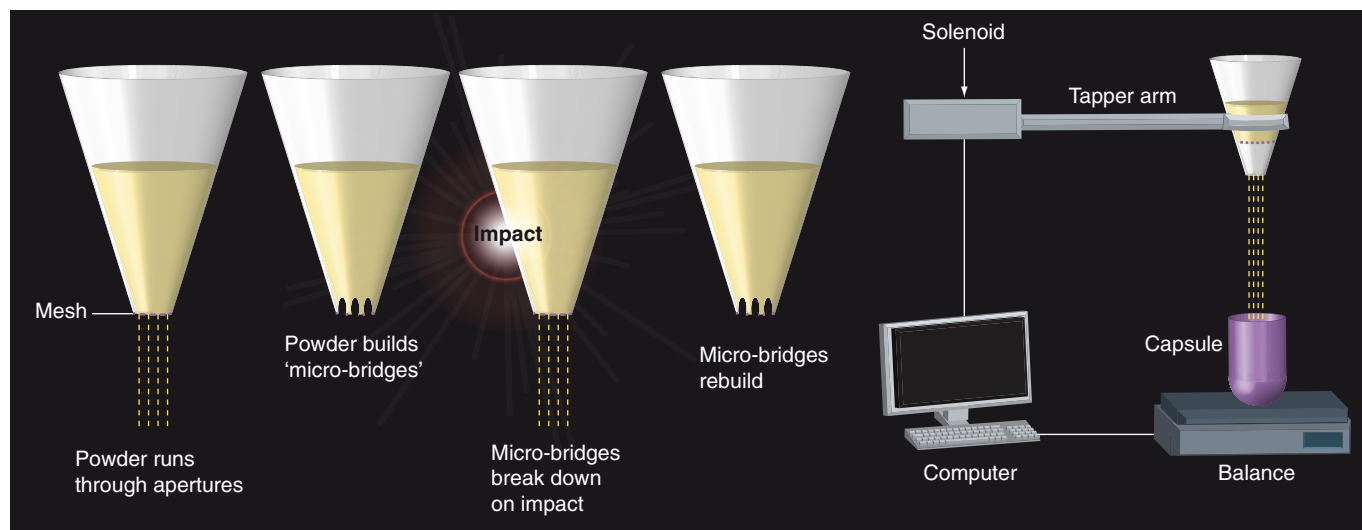


Figure 3. Xcelodose® system methodology.

the fingers to form plugs. At the sixth station, the fingers, contained in a transfer block, push the powder plugs down and out of the disc into capsule bodies as they pass underneath the hopper. The capsule caps are then rejoined with the capsule bodies.

Tamp filling systems can be used for filling powder masses over a similar weight range and RSD as compaction- and vacuum-based dosator systems. The technology is also suitable for small scale Phase I clinical trials through to full-scale manufacturing.

Tamp fillers are best suited for powder masses down to approximately 25 mg. This lower limit can represent a serious limitation for highly potent compounds, in particular those requiring only a small quantity of lactose for stability reasons, and all the attendant issues noted earlier in the development of a lactose-blended formulation.

There is little published information on the different properties between tamp- and dosator-filled capsules for DPI applications, but one report suggests that formulations should have different flow criteria for successful filling as

a higher degree of formulation compaction is required for dosator-based filling systems [12]. In some cases it was found that dissolution profiles for the same formulation filled on the two machines with equivalent compression forces were different, although this has not been translated into a meaningful effect for inhalation formulations. However, it may be concluded that some inhalation powder formulations for use in DPIs may benefit from being filled using tamp filling and others by using dosator technologies.

### 'Pepper-shaker' or 'pepper-pot' principle of dosing

A more recent innovation is the 'pepper-shaker' or 'pepper-pot' principle of capsule dosing [13] and an example of equipment that uses this dosing method is the Xcelodose® 600 Precision Powder **Microdosing** System (Capsugel, Bornem, Belgium). This system works on the principle that when an inverted pepper shaker is tapped it will dispense a uniform amount of powder on each occasion that the container is tapped (**FIGURE 2**). The size of the holes in the shaker is of course vitally important in how much powder is dispensed per tap (**FIGURE 3**).

This microdosing system utilizes a dispensing head filled with powder which contains a mesh of holes of specific diameter and configuration (**FIGURE 4**). Unlike dosator- and tamp-filling systems, a powder bed is not required and this leads to a significant reduction in waste powder as all the powder is able to pass through the dispensing head directly into a capsule. After a single discrete dispensing event (a tap), the powder forms micro-bridges across the holes in

#### Key Term

**Microdosing:** Dosing of powders in the milligram range and below.



Figure 4. Xcelodose® system dispense heads.



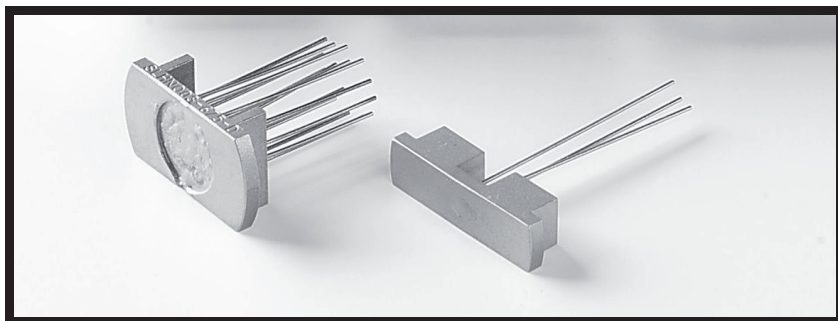
the mesh plate and powder will not be released from the dispensing head until the head is tapped again.

To achieve accurate and monitored dosing, the capsule base is placed on a seven-place microbalance that is tared to zero before dispensing commences. The head is attached to a mechanism incorporating a tap actuator and the process is overseen by a real-time control system. The control system sends signals to the actuator, which then tap the dispense head, thus allowing powder to be discharged into the capsule. The amount of powder dispensed is a function of the particle size and flow properties of the drug formulation, the size and number of holes in the dispensing head, and of the number of taps the dispensing head receives. When the target fill weight has been achieved the tap process ceases and the actual fill weight is logged by the control system. The capsule is then automatically moved to be replaced by the next empty capsule on the microbalance. The filled capsule is closed and any capsule with a fill weight outside the range set by the operator can be rejected automatically. The weight of contents of each capsule is recorded allowing full traceability of samples.

Using the pepper-shaker principle, capsules can be accurately dosed with powder over the range of 0.1 mg up to several hundred milligrams [14] in both gelatin and HPMC capsules over the full capsule size range (size 5 to 000). The RSD of this type of dosing system is typically 2% or less and the Xcelodose 600 S Precision Powder Microdosing System can be used to fill up to 600 capsules per hour making this type of technology ideal for producing capsules for Phase I and II clinical studies.

A major advantage of using the pepper-shaker principle is that the system can dose very small amounts of powders into capsules for use in a DPI. For example, using this method, capsules have been dosed with 1 mg of salbutamol sulfate with an RSD of 2.6% powder weight and a 10-mg blend of salbutamol sulfate and lactose with an RSD of 1.46% powder [15]. Published data indicate that dispensing drug masses as low as 10 µg are also feasible and thus can be a very cost-effective method of dosing capsules with very small amounts of expensive or potent APIs [16].

An additional benefit of using this powder dosing technology is that it does not require powder compaction to transfer the powder to the capsule. For example, a preprocessing step



**Figure 5. Xcelodose® system stainless steel dispense fingers for use with cohesive active pharmaceutical ingredient powders.**

could be undertaken whereby the powder to be dispensed is sieved or milled before adding to the dispensing hopper to ensure any powder agglomeration in the dispense head is kept to a minimum [17]. This additional step is a nonessential part of the process and allows enhancement of results rather than necessity for obtaining acceptable results. Using gravimetric methods the powder dispensed has a known weight, whereas volumetric dosing does not take into account nonuniformity of powder so the final weight may vary accordingly. Furthermore, during capsule dosing, dispense 'fingers' (FIGURE 5) can be used within the dispense head to allow any agglomerated API powder to be broken down during the dispensing process. The filling equipment can be fitted with a unit to control relative humidity (FIGURE 6) and filling can be performed under conditions where the relative humidity is less than 5%, thus preventing hygroscopic compounds from absorbing moisture during the capsule-filling process. This ensures that the powder within the capsule is less likely to form



**Figure 6. Xcelodose® RH Control Unit for controlling relative humidity.**

aggregates and is maintained as a free-flowing powder. Maintaining the free-flowing properties of the dispensed powder within the capsule better ensures the release of powder from the capsule into the inhaler when the capsule is pierced, thereby better controlling both the emitted dose and the fine particle fraction of the dose discharged from the DPI.

### Future perspective

Using this pepper-shaker or pepper-pot technology potentially allows the filling of capsules with small quantities of API without the need for blending with lactose or other carrier compounds. This has the potential to eliminate the need for costly formulation development studies for drugs in early clinical evaluation, although in

## Executive summary

### Dosator technology

- Dosator heads with mechanical compaction and discharging to fill capsules
- Uses powder bed that can lead to compound wastage
- Doses gelatin and hydroxypropyl methylcellulose (HPMC) capsules with 10–500 mg (relative standard deviation [RSD] 2%)
- Can dose 3000–200,000 capsules per hour
- For small-scale Phase I trials and large-scale manufacturing
- Cannot dose less than 10 mg accurately
- Compacts powders so may cause problems with emitted dry powder inhaler (DPI) dosing

### Vacuum dosators

- Dosator heads with vacuum suction and discharging to fill capsules
- Uses powder bed that can lead to compound wastage
- Doses gelatin and HPMC capsules over similar weight range and RSD as dosator technology
- For small-scale Phase I clinical trials and large-scale manufacturing
- Cannot dose less than 10 mg accurately
- Has to dose blends of active pharmaceutical ingredient (API) and carrier compounds
- Requires time-consuming formulation and stability studies of blends
- Compacts powders so may cause problems with emitted DPI dosing
- Requires humidity controlled room for dosing hygroscopic compounds

### Tamp filling

- Tamping pins that move up and down to transfer a dose into a dosing disc
- Uses powder bed that can lead to compound wastage
- Doses gelatin and HPMC capsules over similar weight range and RSD as dosator technology
- For small-scale Phase I clinical trials and large-scale manufacturing
- Cannot dose less than 25 mg accurately
- Has to dose blends of API and carrier compounds
- Requires time-consuming formulation and stability studies of blends
- Compacts powders so may cause problems with emitted DPI dosing
- Requires humidity controlled room for dosing hygroscopic compounds

### 'Pepper-shaker' or 'pepper-pot' principle dosing

- Dispense head with holes that is actuated to dose into capsule underneath
- Doses gelatin and HPMC capsules (0.1 mg to several hundred milligrams; RSD 1–2%)
- Can dose 600+ capsules per hour with potential to scale-up technology
- Weighs every capsule
- For Phase I and II clinical studies
- Dispenses drug weight as low as 5 µg
- Can dose API directly without carrier compounds
- Allows powders to be free flowing
- Can be fitted with humidity control unit for dosing hygroscopic compounds
- Can fill at less than 5% relative humidity without humidity controlled room

the case of drugs for delivery by the inhaled route, the application of this approach would need to be carefully evaluated to ensure effective drug release from the capsule and its subsequent aerosolization. Dosing capsules directly with microgram amounts of API powder may offer a fast route to Phase I trials for many pharmaceutical and biotechnology companies [101].

It is believed that in 5–10 years time it will be possible to know the actual weight of high dispensed amounts and that this will become a regulatory requirement.

## Disclosure

*Xcelodose® and Vcaps® are Capsugel products and trademarks are retained by Capsugel.*

## Financial & competing interests disclosure

*The author is an employee of Capsugel. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

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